PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/IB2004/051922	International filing date *(day/month/year)* 30.09.2004
Priority date *(day/month/year)* 08.10.2003	
International Patent Classification (IPC) or both national classification and IPC A61K31/4035, C07D209/46, A61P7/02, C07D401/06, C07D413/04	
Applicant NICHOLAS PIRAMAL INDIA LIMITED	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Seymour, L

Telephone No. +49 89 2399-8694

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2004/051922

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 21, 22; all claims with respect to prodrugs; 1,2,4-6 and claims referring thereto (part not comprised in claim 3)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. as above

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2004/051922

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-20

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3,5-9
	No:	Claims	1,2,4,10-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

1. The initial phase of the search revealed a very large number of documents relevant to the issue of novelty of claims 1 and 2 (for examples, see search report). So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). In addition, present claim 1 relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed.

   For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been carried out for compounds according to claim 3, i.e. where there is at least one substituent of formula (5) at R^G.

2. The present claims do not fulfil the requirements of Articles 5 and 6 PCT to such an extent as to render a meaningful search impossible. It is unclear which technical features are necessary to perform the functional term "prodrug" and thus which specific compounds fall within the scope of the present claims. Moreover, this functional definition is a mere invitation to the skilled person to perform a research program in order to find the suitable variants (cf. definition in description p. 15). The invention cannot be carried out over the whole claimed area without imposing an undue burden on the skilled person, and the disclosure is thus considered to be insufficient. Consequently, the search did not include prodrugs of the compounds of formula I.

Re Item IV

This Authority found multiple inventions in this international application, as follows:

1. Claims 1-20
   Compounds of formula I and corresponding syntheses, compositions and uses thereof

2. Claim 21
   Alternative process for introducing a keto substituent at the *ortho* position of

phenols.

3. Claims 22
Alternative process for introducing a keto substituent at the *para* position of phenols.

The problem underlying the first group lies in the provision of further fibrinogen receptor antagonists (see present description, p. 1, lines 5 - 9), whereas the problems underlying groups 2 and 3 lies in the provision of alternative syntheses of keto-substituted phenols. Two different problems are thus addressed that are not so linked to form a single general inventive concept (Rule 13.1 PCT).

The only feature common to the processes of groups 2 and 3 is that keto-substituted phenols are produced in both cases. Since such compounds are well known in the art (see e.g. WO-A-02 085855, scheme CO-1), it follows that this feature cannot be considered as being a special technical feature within the meaning of Rule 13.2 PCT. Groups 2 and 3 are therefore also not linked by a single general inventive concept (Rule 13.1 PCT).

Re Item V

1. Reference is made to the following documents:
D1: EP-A-0 655 439
D2: WO-A-02 085855 (family member, P-document: EP-A-1 391 451)
D3: EP-A-0 540 334 D4: US-A-3 997 572
D5: DD-A-66 175 D6: GB-A-989 917
D7: J. Med. Chem., vol. 29, no. 8, 1986, pages 1476-1482
D8: J. Med. Chem., vol. 35, no. 24, 1992, pages 4542-4548

2. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 2, 4 and 10-20 is not new in the sense of Article 33(2) PCT:

Documents D2 discloses numerous imino-isoindole derivatives falling within the scope of present claims 1, 2 and 4 (for claim 4 see numerous compounds e.g. example 546 containing a phenoxy acetic acid moiety or homologues thereof; cf. present formula (5)). The compounds of present claim 3, 5 and 6 differ from those

of D2 because Y^1/Y^2 are =O/S.

The compounds of D3 wherein X is a cyclic moiety are considered to fall within the scope of claims 1 and 2 owing to the passage in the present description (p. 13, lines 4-8) that alkyl groups, unless stated otherwise, may be optionally substituted. Thus, many of the compounds in claim 4 of D3 fall within the scope of present claims 1 and 2 (cf. present R^A is $-C(=O)-NR^1R^2$ wherein R^1 is a substituted alkyl). The compounds of D3 are fibrinogen receptor antagonists (see claim 13).

Documents D4 - D8 disclose a number of pharmaceutically active compounds falling within the scope of present claims 1 and 2 (see references in search report).

3. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of the present claims does not involve an inventive step in the sense of Article 33(3) PCT.

Document D1, which is regarded as being the closest prior art, discloses fibrinogen receptor antagonists (p. 1, lines 23-26). Formula I of D1 overlaps with present formula I. D1 teaches the presence of a 5,6-bicyclic scaffold whereby the 5-membered ring is attached to an acidic group via an optional linker and the 6-membered ring is attached to a basic group via an optional linker. The present exemplified 1-oxo-1,3-dihydroisoindol-2-yl moiety is specifically suggested in D1 (see p. 17, line 45). It would therefore have been obvious for the person skilled in the art, faced with the problem of providing further fibrinogen receptor antagonists, to further modify the exemplified compounds of D1 according to the above teaching in order to arrive at the present compounds.

An inventive step cannot therefore be acknowledged, in the absence of evidence showing that substantially all the claimed compounds have an unexpected property or improved activity with respect to the structurally closest prior art compounds of D1, attributable to the distinguishing feature of the invention.